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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/646,984	09/25/2000	Donn Nelton Rubingh	7070	3865

27752 7590 03/17/2004

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EXAMINER

MOORE, WILLIAM W

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 03/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/646,984	RUBINGH ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 20 August 2003.
- 2a) This action is **FINAL**.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1,2 and 11-28 is/are pending in the application.
- 4a) Of the above claim(s) 17,19,23,25 and 28 is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1,2,11,12,18,20,22,24,26 and 27 is/are rejected.
- 7) Claim(s) 13-16 and 21 is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All
  - b) Some \*
  - c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) <input type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____ .
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ .	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
	6) <input type="checkbox"/> Other: _____ .

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## DETAILED ACTION

*Response to Amendment*

Applicant's Amendment D filed August 20, 2003, has been entered. Amendments to claims 1, 12, 13, 14, and 24 therein overcome the rejection of record under 35 U.S.C. § 112, second paragraph, of claims 1, 2 and 11-16, 18, 20-22, 24, 26 and 27 stated in the Office Action mailed May 20, 2003. The Office Action mailed May 20, 2003, agreed that the Terminal Disclaimer filed May 7, 2003, is effective in avoiding the nonstatutory double patenting rejection of claims 1, 2, 11-16, 18, 20, 21, 24 and 26 herein over claims in a copending application which has since become U.S. Patent No. 6,586,224 on July 1, 2003. Claims 1, 2, and 11-28 remain in this application where claims 17, 19, 23, 25, and 28 were previously withdrawn from consideration as being drawn to non-elected species of modified subtilisin proteases.

*Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1, 2, 11, 12, 18, 20, 22 and 27 are for reasons of record rejected under 35 U.S.C. § 103(a) as being unpatentable over Bryan et al., U.S. Patent No. 5,567,601, of record.

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Applicant's arguments filed August 20, 2003, have been fully considered and are persuasive with respect to the subject matters of the specific deletion-modified subtilisins described by claims 13-16 and 21. The rejection of record is, however, maintained with respect to claims 1, 2, 11, 12, 18, 20, 22 and 27 because Applicant's arguments at 5 pages 5-7 of the Amendment filed August 20, 2003, are not persuasive in establishing that one of ordinary skill in the art at the time the invention was made would have failed to appreciate teachings at col. 4 of Bryan et al. that their "invention provides subtilisin mutants which comprise one or more deletion . . . mutations which provide for the elimination of calcium binding" and that "[i]n the case of subtilisin BPN', the subtilisin 10 mutants will preferably comprise one or more . . . deletion . . . mutations" in addition to their "most preferred" deletion "of amino acids 75-83" in the amino acid sequence of the mature subtilisin BPN'. Indeed, Bryan et al. claim amino acid deletions beyond their "most preferred deletion" at positions that correspond to positions 70-74 in the amino acid sequence of subtilisin BPN'. See claim 1 of Bryan et al. describing "a deletion of 15 amino acids corresponding to amino acid positions 75-83 of the mature subtilisin BPN' . . . and . . . one or more additional, stabilizing, mutations comprising amino acid deletions . . . in at least one region [including the] amino acid positions 70-74".

Bryan et al. thus clearly teach that deletions in the region of amino acids 70-83 in subtilisin BPN' that disable calcium binding yet result in a proteolytically active subtilisin, 20 i.e., deletions embraced by claims 1, 2, 11, and 12 herein, are their invention. An absence of specific exemplifications by Applicant of each and every embodiment of claims 1, 2, 11 and 12 herein does not detract from Applicant's teachings any more than an absence of specific exemplifications of each and every deletion embodiment claim 1 of Bryan et al. does not detract from the ability of their teachings to guide and motivate one 25 of ordinary skill in the art at the time the invention was made to make the further deletions

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they teach. Because claim 1 of Bryan et al. further embraces other "stabilizing, mutations comprising amino acid . . . substitutions . . . at . . . the  $\beta$ -ribbon amino acid positions 202-219", and because claims 2-6 and 11 of Bryan et al. particularly recite six of the amino acid substitutions recited by claim 20 herein, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare modified subtilisins of claims 18 and 20 herein that also comprise any of these six amino acid substitutions to compensate for reduced thermal stability of the subtilisin mutants lacking one or more of the native amino acids at positions corresponding to positions 70-83 of subtilisin BPN'. Bryan et al. additionally teach that their subtilisin BPN' mutants should be used in detergent compositions, which are cleaning compositions, designed for use with water having a low concentration of calcium ion, rendering the subject matter of claim 22 obvious to one of ordinary skill in the art at the time the invention was made. Preparation of a mutant gene of claim 27 herein would also have been obvious to one of ordinary skill in the art at the time the invention was made because Bryan et al. teach the preparation of nucleic acid sequences encoding their altered subtilisins, hence "mutant genes", see claims 13 and 14 of Bryan et al. and because they used such mutant subtilisin genes in order to recombinantly produce modified subtilisins, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare such mutant genes encoding modified subtilisins of claim 1 herein to produce them recombinantly in a transformed host cell as Bryan et al. had done.

Applicant again presents a corollary argument at pages 6-7 filed August 20, 2003, asserting that different motivations experienced by Bryan et al. and by Applicant for making amino acid sequence deletions at the same subtilisin BPN'-correspondent positions 70-84 could alter the analysis of obviousness under 35 U.S.C. § 103(a). This position is mistaken where Bryan et al. are not "protecting the protease from metal

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chelators", but instead are modifying subtilisins to permit them to function in very low concentrations of calcium ions, and one of ordinary skill in the art need only experience sufficient motivation in the teachings of the prior art to make an invention embraced by the claims rejected herein, not a motivation that is identical to that experienced by a  
5 subsequent applicant for patent. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation that using the guidance of Bryan et al. would permit the production subtilisin variants, in addition to their "most preferred variant", that are less dependent on calcium ion for stability yet have adequate stability by incorporating the series of stabilizing deletions and/or substitutions at positions that  
10 Bryan et al. teach should be included when altering the calcium binding site region, and the products of this motivation are indistinguishable from products described by the claims rejected herein. The rejection of record is maintained.

15 **Claims 24 and 26 are for reasons of record rejected under 35 U.S.C. § 103(a) as being unpatentable over Bryan et al. as applied to claims 1, 2, 11, 12, 18, 20, 22 and 27 above, and further in view of Powell et al., U.S. Patent No. 6,060,546, of record.**

Applicant's arguments filed August 20, 2003, have been fully considered but they are not persuasive. Applicant suggests that one of ordinary skill in the art at the time the invention was made would have perceived the teachings of Bryan et al. to be  
20 directed to making amino acid deletion and substitution mutations to produce modified subtilisins more stable in an "industrial environment" only. Yet anyone of ordinary skill in the art at the time the invention was made would have appreciated that personal care compositions, such as shampoos and skin cleansers, may be used by the consumer in both "soft" water environments, where calcium concentrations may be low, and "hard"  
25 water environments, where calcium concentrations may be high, as well as appreciating that personal cleansing compositions may be formulated with metal chelators present, thus would have found the teachings of Bryan et al. applicable to preparing modified

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subtilisins suitable for such uses and such formulations. Applicant provides no reason why one of ordinary skill in the art at that time would have expected that subtilisin variants suggested by Bryan et al. might be unsuitable for incorporation in personal care compositions, particularly when destined for use with "soft" water or in a solution with a low calcium ion concentration such as the non-aqueous solution of Powell et al., where the artisan would have had a reasonable expectation, on the basis of the teachings of Bryan et al., that it would exhibit better stability than the native protease taught by Powell et al. The rejection of record is maintained.

*Conclusion*

10        Claim 13-16 and 21 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

15        A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

20        Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at 571.272.0928. The fax phone numbers for all communications for the organization where this application or proceeding is assigned remains 703.872.9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

25        William W. Moore  
30        March 10, 2004

  
NASHAATT NASHED PH.D.  
PRIMARY EXAMINER